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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,913	08/06/2001	Zuomei Li	MET-021US1	8110
32254 7590 12/08/2009 KEOWN & ZUCCHERO, LLP 500 WEST CUMMINGS PARK SUITE 1200 WOBURN, MA 01801				
EXAMINER				
VAKILI, ZOHREH				
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1614				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/817,913

Applicant(s)

LI ET AL.

Examiner

ZOHREH VAKILI

Art Unit

1614

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 July 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 45-48, 50, 51, 53 and 54 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 45-48, 50, 51, 53 and 54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/ISA/C3)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

Claims 45-48, 50-51, 53-54 are presented for examination.

Applicant's Amendment filed July 13, 2009 has been received and entered into the present application. Claims 45-48, 50-51, 53-54 are pending and are herein examined on the merits.

Applicant's arguments, filed July 13, 2009 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 102 (Maintained)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 45-48 are rejected under 35 U.S.C. 102(b) as anticipated by Jones et al. (Nature Genetics, 1998, of record).

Claim 45 is directed to a method of modulating cell proliferation in a cell comprising the step of contacting the cell with an agent that inhibits one or more histone deacetylase isoforms. Claims 46-48 limit claim 45 to proliferation that is neoplasia and recite specific histone deacetylase isoforms.

Jones et al. disclose contacting a cell with TSA, a small molecule inhibitor of histone deacetylase. The use of small molecule inhibitor inherently would inhibit all or some HDAC isoforms. Jones et al. do not explicitly state that proliferation of the cells is inhibited, but the method of Jones et al. comprises all of the steps of the claimed method and, absent evidence to the contrary, would be expected to inhibit proliferation, including neoplastic proliferation.

Thus, Jones et al. disclose all limitations of and anticipate claims 45-48.

Claims 45-48, 50-51, and 53-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Kwon et al. (Proc. Natl. Acad. Sci. USA 1998, vol. 95, pages 3356-3361).

Kwon et al. disclose a small molecule inhibitor which inhibits **histone deacetylase-I (HDAC-1)** (as recited in claims 47-48 and 53-54), which has the effect of inducing the reversion of cells transformed with a known oncogene from the morphology of a transformed cell to that of a normal cell. The teaching of the inhibition of a specific

histone deacetylase isoform, HDAC-1, reads on the limitation of inhibiting specific HDAC isoforms, but less than all HDAC isoforms.

Thus, Kwon et al. disclose all limitations of and anticipate claims 45-48, 50-51, and 53-54.

Claims 45-48 are rejected under 35 U.S.C. 102(e) as being anticipated by MacLeod et al. (US 2003/0078216).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim 45 is directed to methods of inhibiting cell differentiation or proliferation, including neoplastic cell proliferation in an animal, by administering an agent that inhibits one or more specific histone deacetylase isoforms. Claims 46-48 limit claim 45 to neoplastic cell proliferation and recite specific histone deacetylase isoforms.

MacLeod et al. disclose a method of inhibiting cell proliferation by inhibiting histone deacetylase using antisense oligonucleotides. MacLeod et al. further disclose that the antisense oligonucleotides are targeted to the histone deacetylase isoforms recited in claim 47 and that the method may be performed in humans.

Thus, MacLeod et al. disclose all limitations of and anticipate claims 45-48.

Claims 45-48, 50-51, and 53-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Kwon et al. (Proc. Natl. Acad. Sci. USA 1998, vol. 95, pages 3356-3361).

Kwon et al. disclose a small molecule inhibitor which inhibits **histone deacetylase-I (HDAC-1)** (as recited in claims 47-48 and 53-54), which has the effect of inducing the reversion of cells transformed with a known oncogene from the morphology of a transformed cell to that of a normal cell. The teaching of the inhibition of a specific histone deacetylase isoform, HDAC-1, reads on the limitation of inhibiting specific HDAC isoforms, but less than all HDAC isoforms.

Thus, Kwon et al. disclose all limitations of and anticipate claims 45-48, 50-51, and 53-54.

Claim Rejections - 35 USC § 103 (Maintained)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sambucetti et al. (Journal of Biological Chemistry 1999, vol. 274, pages 34940-34947), Taunton et al. (Science 1996, cited on IDS), Baracchini et al. (US 5,801,154) and Bennett et al. (US 5,998,148).

Claim 45 are directed to methods of inhibiting cell differentiation or proliferation by administering an agent that inhibits one or more specific histone deacetylase isoforms. Claims 46-48 limit claim 45 to neoplastic cell proliferation and recite specific histone deacetylase isoforms.

Sambucetti et al. teach that inhibition of histone deacetylase using the tetrapeptide inhibitor TPX inhibits tumor cell proliferation. Sambucetti et al. do not teach the use of antisense oligonucleotide inhibitors of histone deacetylase.

Taunton et al. teach the isolation and sequence of **histone deacetylase-I (HDAC-1)** (as recited in claims 47-48 and 53-54). The teaching of the inhibition of a specific histone deacetylase isoform, HDAC-1, reads on the limitation of inhibiting specific HDAC isoforms, but less than all HDAC isoforms.

Baracchini et al. teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al provide specific embodiments of such modifications at columns 6-8 and in Example 1. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture. Table 1 exemplifies the successful practice of general antisense design taught at columns 8- 10. Column 4 teaches various carriers for antisense delivery. Baracchini et al. also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett et al. are considered to parallel those of Baracchini et al. Bennett et al. teaches general antisense targeting guidelines at columns 3-4. Bennett et al. also teaches targeting 5'-untranslated regions, start codons, coding regions, and 3'-untranslated regions of a desired target. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 6-7 teach that preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate

linkages, among others. Columns 7-8 teach that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. Bennett et al. also teach one of ordinary skill to modify nucleobases in antisense oligonucleotides, including the teaching of 5-methylcytosine (col. 8-9), and also to use chimeric antisense oligonucleotides (col. 9-10). Bennett et al. teach that the above modifications are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. Columns 10-24 teach numerous carriers for antisense oligonucleotides. Table 1 teaches the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification). Thus, Bennett et al. is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence taught by Taunton et al. to generate antisense sequences as taught by Baracchini and Bennett for inhibition of **histone deacetylase-I** expression for the purposes of treating neoplastic cells via inhibition of **histone deacetylase-1 as taught by Sambucetti et al.** One would have been motivated to create such compounds because Sambucetti et al. teach that their inhibitor of histone deacetylase can be used to inhibit tumor cell proliferation. Furthermore, both Bennett and Baracchini et al. teach that antisense molecules can be easily made and used to inhibit any target so long as the sequence is known, and provide for their methods of use in humans. Therefore, one of ordinary skill in the art would have been motivated to use the sequence histone

deacetylase and the inhibition of a specific histone deacetylase, HDAC-1 of Taunton et al. to develop antisense inhibitors for the purpose of treating neoplastic cells, because Sambucetti et al. teach that inhibition of **histone deacetylase-I (HDAC-1)** can inhibit tumor cell proliferation.

Finally, one would have a reasonable expectation of success given that Baracchini et al. and Bennett et al. provide a detailed blueprint for making and using modified antisense compounds targeted to a target gene, the sequence of which is provided by Taunton, and the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention of claims 45-48 would have been prima facie obvious as a whole to one of ordinary skill in the art at the time the invention was made.

Response to Argument

Applicant's remarks have been fully and carefully considered in their entirety, but fail to be persuasive. Specification does not define or give any example as what the Applicant is referring to as small molecule inhibitors. The specification clearly states that the agents used to perform the claimed method include antisense oligonucleotides and small molecule inhibitors. Since, it appears that the Applicants were not in possession of small molecule inhibitors, Examiner has interpreted the invention as being limited to including antisense oligonucleotides as the agent. Applicant further

traverses MacLeod et al. indicating the instant claims are not directed to antisense oligonucleotides, wherein the agent is a histone deacetylase small molecule inhibitor. Examiner does not agree antisense oligonucleotides are small or short in length nucleotides, therefore it meets the limitation of small molecule inhibitor.

Applicant further indicates that Jones et al. disclose contacting a cell with TSA, a small molecule inhibitor of histone deacetylase (HDAC). However, Applicant traverses the rejection indicating that TSA is a pan inhibitor (i.e., it is non-specific) and inhibits all HDAC isoforms. This argument is not persuasive, there is no factual data showing that TSA is a non-specific inhibitor and inhibits all HDAC isoforms. Applicant also argues that Kwon teaches inhibitors that inhibit all isoforms. Again, this argument is not persuasive, there is no factual data showing this allegation. In fact, Kwon et al. disclose a small molecule inhibitor which inhibits histone deacetylase-I (HDAC-1).

Applicant's amendments and remarks have been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

Conclusion

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner 1614

November 13, 2009

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614